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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/241,653	02/02/99	WAGNER H	C1041/7002-H

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HELEN C LOCKHART
C/O WOLF GREENFIELD & SACKS PC
FEDERAL RESERVE PLAZA
600 ATLANTIC AVENUE
BOSTON MA 02210-2211

EXAMINER	
SCHMIDT, M	
ART UNIT	**PAPER NUMBER**
1635	10

DATE MAILED: 03/30/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/241,653	Wagner et al.
Examiner	Group Art Unit
Schmidt	1635

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Response

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-65 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-65 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☒ Notice of References Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

DETAILED ACTION

Specification

1. The specification is objected to on page 39, lines 12-21, for missing SEQ ID Nos. Furthermore, if the missing SEQ ID Nos. are not presently included in the paper copy and computer readable version of the sequence listing, then a new sequence listing and CRF will also be required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 12, 41, 50 and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12, 41, 50 and 63 are drawn to the methods of claims 1, 27, 42 and 51 respectively, wherein " X_1X_2 are nucleotides selected from the group consisting of GpT, GpG, gpA and ApA and X_3X_4 are nucleotides selected from the group consisting of TpT, CpT or GpT". The claims as written lack antecedent basis for the X_1X_2 and X_3X_4 language since the parent claims do not contain these structures as claimed.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the administration of certain oligonucleotides in whole organisms for specific functions, does not reasonably provide enablement for the scope of such oligonucleotides for the functions broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to: (1) methods of inducing an *antigen-specific immune response* via administration to a subject an oligonucleotide having a sequence including "at least the following formula: 5'$X_1CGX_2$3'" wherein the oligonucleotide includes at least 8 nucloeotides wherein C and G are unmethylated and wherein X1 and X2 are nucleotides and exposing the subject to an antigen for a period of time (at least 3, 4, 7, 15, or 30 days) after the oligonucleotide is administered to the subject to produce an antigen-specific immune response (claims 1-5). The dependent claims specify the antigen as a nucleic acid encoding an antigen (claim 13), cells, cell extracts, proteins, polysaccharides, polysaccharide conjugates, lipids, glycolipids, carbohydrate, viral extracts, bacteria, fungi, parasites, and allergens, or derived from an infectious organism such as bacteria, viruses or fungi (claims 14-16). The dependent claims 17-21 specify that the subject is activelyexposed to the antigen, wherein the antigen is delivered in conjuction with a colloidal

dispersion system such as macromolecular complexes, nanocapsules, microspheres, beads, and lipid-based systems such as oil-in-water emulsions, micelles, mixed micelles or liposomes, wherein an adjuvant is also administered in conjuction with the antigen. Claims 22-25 specify that the subject is passively exposed to the antigen, wherein the subject is at risk of developing cancer, an allergic reaction, or is an asthmatic. Claim 26 specifies the antigen specific immune response is a Th1 type immune response. Claims 6-12 further specify different structures of the oligonucleotide of claim 1;

(2) methods for *increasing platelet counts in a subject having thrombocytopenia* comprising: administering to a subject having (non-chemotherapeutic induced) thrombocytopenia an oligonucleotide having the sequence including "at least the following formula: 5'$X_1CGX_2$3'" wherein the oligonucleotide includes at least 8 nucloeotides wherein C and G are unmethylated and wherein X1 and X2 are nucleotides, in an amount effective to increase platelet counts in the subject (claim 27). Dependent claims 28-34 specify the following limitations: the oligonucleotide is administered in an amount effective to increase platelet counts in the subject by at least 10,000 platelets per microliter, or 20, 000 platelets per microliter, or to increase the platelet counts in the subject by 100%; wherein the thrombocytopenia is a drug-induced thrombocytopenia, or is due to an autoimmune disorder such as idiopathic thrombocytopenic purpura, or results from accidental radiation exposure or from therapeutic radiation exposure. Claims 35-41 further specify different structures of the oligonucleotide of claim 27;

(3) methods for *treating a subject at risk of developing thrombocytopenia* comprising: administering to a subject at risk of developing thrombocytopenia an oligonucleotide, having a sequence including "at least the following formula: 5'$X_1CGX_2$3'"wherein the oligonucleotide includes at least 8 nucloeotides wherein C and G are unmethylated and wherein X1 and X2 are nucleotides, in an amount effective to prevent a decrease in platelet counts ordinarily expected under platelet-depleting conditions in the subject when the subject is exposed to platelet-depleting conditions (claim 42). Dependent claim 43 specifies the subject at risk of developing thrombocytopenia as having a disorder treated with platelet suppressive drugs. Dependent claims 44-50 further specify different structures of the oligonucleotide of claim 42;

(4) methods for treating anemia comprising administering to a subject having anemia an oligonucleotide, having a sequence including "at least the following formula: 5'$X_1CGX_2$3'"wherein the oligonucleotide includes at least 8 nucloeotides wherein C and G are unmethylated and wherein X1 and X2 are nucleotides, in an amount effective to induce erythropoiesis in the subject (claim 51). Dependent claims 52-52-54 specify that the oligonucleotide of claim 51 is administered in an amount effective to increase erythroblast counts in the subject by at least 10%, 20%, or 100%. Dependent claims 55-56 specify that the anemia is a drug-induced anemia, or selected from the group consisting of an immunohemolytic disorder, genetic disorders such as hemoglobinopathy and inherited hemolytic anemia, inadequate production despite adequate iron stores, chronic disease such as kidney failure, or chronic inflammatory disorder such as rheumatoid arthritis. Claims 64-65 specify that the anemia is an anemia resulting from accidental

radiation exposure or resulting from therapeutic radiation exposure. Claims 57-63 further specify different structures of the oligonucleotide of claim.

Thus all claims comprise administration of an oligonucleotide to a whole organism having a sequence including "at least the following formula: 5'$X_1CGX_2$3'"wherein the oligonucleotide includes at least 8 nucloeotides wherein C and G are unmethylated and wherein X1 and X2 are nucleotides. The claims differ in the functionality claimed and in the scope of dependent claims specifying various limitations to the modes of delivery and "effective" amounts of oligo delivered to achieve such functions. Additionally, the functionality claimed differs in the treatments claimed and the first group of methods specifies co-delivery of an antigen. The depended claims specifying limitations of the administered oligo specify the length of the oligo as 8-100 bases, the bases as having phosphate backbone modifications, and wherein the sequence is 5'$X_1X_2CGX_3X_4$3' (claims 10, 39, 48 or 61) where the X_1X_2 nucleotides are from the group consisting of GpT, GpG, GpA or ApA, and the X_3X_4 nucleotides are from the group consisting of TpT, CpT, or GpT; or the sequence is at least 5'TCNT$X_1X_2CGX_3X_4$3' where N is a nucleic acid from 0-25 nucleotides.

The specification as filed teaches a review of the state of the art for the effects seen in whole organisms upon administration of unmethylated CG containing sequences. See pages 1-8 especially. On page 8 of the specification, applicant states that "The prior art as a whole implies that Th2 driven responses are strongly predisposing for extramedullary hematopoiesis. CpG-ODN injection is Th1-biasing and Th-2 suppressive. In addition, IFN-gamma, the hallmark Th1

cytokine has been shown to induce hematopoiesis. Thus the prior art would not suggest to one of skill in the art that the cytokine reprotoir released by CpG-ODN injection will lead to hematopoiesis. To the contrary, ODN administration has been shown to lead to thrombocytopenia, anemia, and neutropenia. Additionally the administration of IL-12, a central cytokine in CpG-ODN effects, induces thrombocytopenia. The phenomenon of splenomegaly has been repeatedly correlated with B cell activation rather than hematopoiesis. The present invention relates to methods for inducing hematopoiesis to treat immune system disorders. In one aspect the invention relates to a method for inducing an antigen-specific immune response. The method is based on the finding that a CpG oligonucleotide can be used to induce remodeling of the immune system by regulating hematopoiesis. After a CpG oligonucleotide and antigen are administered together to a subject an initial immune response occurs. It has been discovered according to the invention that this initial immune response declines rapidly and a new immune response develops after approximately 48 hours. Unexpectedly, when antigen is administered 48 hours or more after the administration of CpG an antigen specific immune response will be mounted to the antigen. This immune response is due to a repopulation of lymph nodes and/or spleen with primed immune cells."

By way of example the specification teaches increased spleen weight, increased numbers of GM-CFU cells, and induced blood and cell resistance to 5-FU in mice for instance. The specification asserts that the results of these experiments correlate to a novel application of CpG containing oligonucleotides to induce any antigen-specific immune response, increasing platelet

counts in a subject having thrombocytopenia, treating a subject at risk of developing thrombocytopenia and/or treating anemia.

There are several areas of unpredictability in the art which preclude a correlation between the guidance taught in either the art or the specification with the claims as broadly written.

The following factors are considered unpredictable in the art: (1) the sequence and structural composition of the CpG containing motif is considered to play an important role in the immuno-stimulatory effects of the oligonucleotide (see for instance Zhao et al., page 180: "This observation indicates that the stimulatory effects are dependent upon particular sequences of the oligonucleotide but independent of whether the oligonucleotide is antisense, sense, or scrambled with respect to their respective target genes.... Kreig et al. Reported that optimal B cell activation requires a DNA motif in which an unmethylated CpG dinucleotide is flanked by two 5' purines and two 3' pyrimidines....Our findings strongly suggest that chemical modifications play an important role in the stimulatory effects. The degree of substitution with thioate linkages in the oligonucleotide can influence the stimulatory activity of the oligonucleotides."); (2) the lack of correlation between mice and other whole organisms for therapeutic results (see for instance Crystal who teaches that "Humans are not simply large mice" for treatment in gene therapy, and specifically in regards to CpG oliognucleotides, note Jones et al. who teaches that "CpG motifs within DNA vaccines appear to provide essential adjuvant activity since immune responses are abrogated in mice if potent motifs are removed or methylated... However, all of these studies were performed in mice, and mice are often more responsive to immune stimulation than primates.

One additional factor that may limit the applicability of these mouse data to humans is the recent finding that CpG motifs are species-specific, with the flanking bases and spacing between adjacent motifs determining whether a given CpG dinucleotide is stimulatory for a given species. While murine immune cells respond to a wide variety of CpG motifs, cells obtained from humans and other primates respond to a much more restricted subset."; Further more, the specification as filed on page 55 notes that "In contrast to humans, mice display a basal hematopoietic activity in the spleen.").

Such unpredictability in the art suggests that one skilled in the art would necessarily practice "trial and error" experimentation to make and use the invention for administration of any CpG containing oligonucleotide for the scope of therapeutic applications as instantly claimed. The quantity of experimentation necessary to practice the invention would require de novo determination of the claimed treatment effects for any random sequence claimed as well as correlated success for the scope of whole organisms claimed (see the unpredictable factors argued above). One skilled in the art would necessarily practice an undue amount of experimentation to make and use the invention as claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *George Elliott, Ph.D.* may be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

George C. Elliott, Ph.D.
Supervisory Patent Examiner
Technology Center 1600

M. M. Schmidt
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